5 Combining diuretic response and hemoconcentration to predict rehospitalization after admission from acute heart failure – lessons from PROTECT and EVEREST

Jozine M. ter Maaten, Mattia A.E. Valente, Kevin Damman, John G. Cleland, Michael M. Givertz, Marco Metra, Christopher M. O'Connor, John R. Teerlink, Piotr Ponikowski, Daniel M. Bloomfield, Gadi Cotter, Beth Davison, Haris Subacius, Dirk J. van Veldhuisen, Peter van der Meer, Hans L. Hillege, Mihai Gheorghiade, and Adriaan A. Voors

Accepted Circulation: Heart Failure

ABSTRACT

Background

Both diuretic response and hemoconcentration are indicators of decongestion and have individually been found to predict rehospitalization after admission for acute HF. This study examines the value of combining diuretic response and hemoconcentration to better predict patients at low risk for rehospitalization after admission for acute heart failure (HF).

Methods

Diuretic response (defined as weight change per 40 mg of furosemide on day 4 after admission) and hemoconcentration (change in hemoglobin at discharge or day 7) were tested both individually and combined to predict the risk of HF and cardiovascular rehospitalization 60 days after hospitalization for acute HF. Analyses were performed in 1180 patients enrolled in the PROTECT trial and validated in 1776 patients enrolled in the EVEREST trial.

Results

Poor diuretic response was associated with low systolic blood pressure, high blood urea nitrogen, and history of coronary revascularisation in both datasets (all $P<0.05$). Hemoconcentration was mainly associated with better renal function ($p<0.05$). Patients who displayed both favourable diuretic response and hemoconcentration had a markedly lower risk of rehospitalization for HF in PROTECT: multivariable HR 0.41, 95% CI 0.24-0.70, $P<0.001$, compared to all other patients. This finding was confirmed in EVEREST: multivariable HR 0.52, 95% CI 0.33-0.82, $p=0.004$, for patients with a favourable diuretic response and hemoconcentration compared to all other patients.

Conclusion

Combining two indicators of decongestion, hemoconcentration and diuretic response improves risk prediction for early rehospitalization after an admission for acute HF, and may provide clinicians with an easy accessible tool to identify low risk patients.

INTRODUCTION

Hospitalization for acute heart failure (HF) is a harbinger of mortality and morbidity.[1-3] The high risk of early readmission after discharge is a particularly significant health care problem for patients and our health care systems. Early readmission is both a medical and financial challenge, as the associated costs are not reimbursed in some countries if the readmission occurs within 30 days after admission. This has forced physicians to pursue a more defensive strategy in which patients are hospitalized for a longer period, in order to try to prevent readmission, further increasing health care costs. Therefore, it is of great importance to detect patients at low risk and understand the pathophysiology behind early readmissions. Identifying patients who may be safely discharged early because of adequate decongestion and a low risk of rehospitalization would also be of significant clinical utility. Recently, several studies have shown that inadequate response to diuretic treatment is particularly related to an increased risk of early readmission after hospital discharge for acute heart failure.[4-7] Similarly, several other studies showed hemoconcentration (i.e. an increase in hemoglobin/hematocrit in response to diuretic therapy during hospital admission) is related to a lower risk of rehospitalization after an acute HF admission.[8-10] Both diuretic response and hemoconcentration provide estimates of the adequacy of decongestion during hospital admission. Therefore, the present study aimed to combine both measures to improve our estimation of adequacy of decongestion and our ability to distinguish between patients at low and high risk of early rehospitalization for acute heart failure.

METHODS

Study design and procedures

The design and main results of PROTECT (Placebo controlled randomized study of the selective adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function) and EVEREST (Efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan) have been published previously.[11,12] In brief, PROTECT and EVEREST were both multinational, prospective, multicentre, randomized, double-blind, placebo-controlled trials in patients with acute HF. PROTECT, which investigated the effects of rolofylline, was a trial with neutral results and enrolled 2033 adult patients with mild to moderate renal dysfunction and acute HF. EVEREST enrolled 4133 patients and investigated the effect of oral tolvaptan on clinical outcomes in patients a reduced ejection fraction hospitalised for worsening heart failure. All patients provided informed written informed consent, and both trials were conducted in accordance with the declaration of Helsinki and approved by local ethics committees at all participating sites.

In PROTECT, heart failure signs and symptoms, serum creatinine and blood urea nitrogen (BUN) were assessed daily until discharge or day 6, and on days 7 and 14. Body weight was assessed from baseline through day 4. Other biochemical and hematologic markers were measured at least at baseline and on days 2, 7 and 14. In EVEREST, biochemical and hematologic markers were assessed at baseline and discharge or day 7, and weight data was collected through discharge. Diuretic administration during hospitalization was recorded in both studies. Glomerular filtration rate was calculated with the simplified MDRD equation.

Diuretic response and hemoconcentration

Diuretic response was defined as weight change on day 4 per 40 mg of furosemide or equivalent as described previously.[5] Loop diuretics other than furosemide were converted into equivalent doses as follows: 40 mg furosemide: 1 mg bumetanide: 20 mg torsemide. Half of the oral dose was used to adjust for biological availability.[5] Hemoconcentration was defined as change in hemoglobin on hospital day 7 or discharge, whichever came first.[10]

Study population

Initial analyses were performed in PROTECT and validated in EVEREST in patients with no missing data on the primary variables of interest. Patients with missing data for diuretic response (PROTECT n=278, EVEREST n= 1421), >20kg weight loss (PROTECT=3, EVEREST n=0),[5] who underwent dialysis through day 4 (PROTECT n=7, EVEREST not recorded) or missing data on hemoconcentration (PROTECT n=0, EVEREST n=388) were excluded, resulting in a study population of 1180 patients for PROTECT and 1776 patients for EVEREST. The included populations did not differ greatly from the excluded populations (supplementary tables S1 and S2).

Endpoints

The primary endpoints for this study were HF rehospitalization or renal or cardiovascular rehospitalization within 60 days for PROTECT, and heart failure rehospitalization or cardiovascular rehospitalization within 60 days for EVEREST. Associations with 180-day mortality were also examined in both populations. Endpoints were adjudicated by independent clinical endpoint committees for each trial.

Statistical analysis

Initial analyses were performed in PROTECT and validated in EVEREST. All analyses were performed in the intention to treat population, checking for effects of and interactions with study treatment. Continuous data are summarized as mean±standard deviation or median [interquartile range] depending on distribution. Student's t-test or ANOVA (normal distribution), and Wilcoxon or Kruskall-Wallis (skewed distribution) tests were used for group comparisons as appropriate. Differences in proportions were assessed using Chi-squared tests.

Pearson's correlation coefficient was used to assess correlations. Trends across categories were tested using non-parametric tests for trend for categorical variables, and generalized linear models with polynomial contrasts for continuous variables. Only complete cases were used for all primary analyses; no imputations were performed.

Cox proportional hazards regression was used to examine associations with the endpoints. Multivariable models were corrected for study treatment and clinical covariates from a previously published model developed in PROTECT, to which baseline hemoglobin was added.[13] Covariates were transformed as appropriate, with multiple fractional polynomials used to assess the linearity of associations.

The added value of diuretic response and hemoconcentration for estimating the risk of rehospitalization was assessed by examining gain in Harrell's C-index (a measure of model discrimination, higher values are better), using likelihood ratio tests for nested survival models, and assessment of continuous net reclassification improvement (NRI, a category-independent measure quantifying the degree of improvement in model-based risk estimates obtained by adding a marker to a model). Tests are two-tailed, and an unadjusted p-value < 0.05 was considered statistically significant. All analyses were performed using R: A Language and Environment for Statistical Computing, version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Baseline characteristics for both PROTECT and EVEREST populations are presented in table 1. Patients in PROTECT were more often female, were older and co-morbidities were more common than in EVEREST. Patients in PROTECT also showed more signs of congestion, such as edema, orthopnea and elevated JVP. Renal function was worse, hemoglobin levels lower and B-type Natriuretic Peptide (BNP) levels higher. Median diuretic response was -0.36 [-0.77 - -0.13] kg/40 mg furosemide (PROTECT) and -0.30 [-0.79 - -0.03] kg/40 mg furosemide (EVEREST). Median hemoconcentration was 0.20 [-0.50 – 0.26] g/dL (PROTECT) and 0.20 [-0.40 – 0.90] (EVEREST), with 58% of patients in PROTECT and 56% of patients in EVEREST displaying a rise in hemoglobin by day 7 or discharge.

Baseline characteristics for the two populations, stratified by tertile of diuretic response, are presented in tables 2a (PROTECT) and 2b (EVEREST). In this subpopulation of the PROTECT, patients with poor diuretic response were more likely to have renal impairment, and had signs of more advanced heart failure, including more frequent device therapy, similar to earlier findings.[5] Similar patterns were seen in EVEREST, although in contrast with PROTECT, some co-morbidities – such as diabetes and myocardial infarction – were not strongly as-

Table 1. Baseline characteristics for patients enrolled in PROTECT and EVEREST

	PROTECT	EVEREST
N =	**1180**	**1776**
Demographics		
Sex (%(n) Male)	67.9 (801)	74.4 (1321)
Age (years)	69.7± ±11.5	65.1±11.3
LVEF (%)	30 [22-40]	30 [22-35]
Systolic Blood Pressure (mmHg)	124.2±17.7	121.8±19.5
Diastolic Blood Pressure (mmHg)	74.4±11.7	74.6±12.5
Heart Rate (beats/min)	80.9±15.5	81.4±16.2
Clinical Profile		
Atrial fibrillation on presentation (%(n))	45.5 (215)	34.5 (613)
Orthopnea ≥ +2 (%(n))	96.1 (1124)	54.8 (956)
Rales > 1/3 lung fields (%(n))	61.7 (728)	82.9 (1450)
Edema ≥ +2 (%(n))	69.8 (824)	62.6 (1112)
Jugular venous pressure ≥ 10 cm (%(n))	41.4 (439)	29.1 (506)
Medical History		
HF hospitalization (%(n))	95.3 (1124)	80.2 (1418)
Hypertension (%(n))	79.5 (938)	70.7 (1255)
Diabetes Mellitus (%(n))	45.1 (532)	36 (639)
Ischemic Heart Disease (%(n))	70 (825)	67.7 (1184)
Myocardial Infarction (%(n))	49.3 (580)	50.6 (898)
CABG (%(n))	20.3 (237)	15.6 (277)
Peripheral Vascular Disease (%(n))	11 (129)	20.9 (371)
Atrial Fibrillation (%(n))	55.3 (649)	45.3 (805)
ICD therapy (%(n))	14.6 (172)	10.5 (187)
Stroke (%(n))	8.6 (101)	11.6 (202)
COPD (%(n))	19.1 (225)	8.4 (149)
Prior Medication Use		
ACE inhibitors or ARB (%(n))	75.4 (890)	85.8 (1519)
Beta blockers (%(n))	76.4 (902)	68.7 (1216)
Mineralocorticoid Receptor Antagonists (%(n))	45.8 (541)	61.5 (1089)
Laboratory Values		
Creatinine (mg/dL)	1.4 [1.1-1.8]	1.2 [1-1.5]
eGFR (mL/min/1.73m2)	51.7±20.2	56.7±20.7
Blood Urea Nitrogen (mg/dL)	29 [22-41]	25 [19-34]
Sodium (mmol/L)	140 [137-142]	140 [137-143]
Potassium (mmol/L)	4.2 [3.9-4.6]	4.3 [4-4.7]
Hemoglobin (g/dL)	12.7 [11.3-14.1]	13.8 [12.3-15]
BNP (mg/dL)	1290.9 [835.1-2411.9]	667.2 [283-1396.8]

Abbreviations: LVEF: left ventricular ejection fraction; HF: heart failure; CABG: coronary artery bypass graft; ICD: implantable cardiac defibrillator; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide.

sociated with diuretic response. Interestingly, BNP levels at admission were not associated with diuretic response in either population.

Hemoconcentration was not strongly associated with clinical characteristics or medical history in either trial population (p for trend = n.s. across tertiles). Patients who hemoconcentrated more did have better renal function, lower BUN levels and lower hemoglobin at baseline (Supplementary tables S3 and S4).

Outcomes

Clinical outcomes for PROTECT and EVEREST are presented in tables 2a and 2b. Rates for all rehospitalization endpoints and mortality were numerically higher in PROTECT compared with EVEREST. In both cohorts, however, a significant trend over tertiles of diuretic response showed higher incidences of adverse outcomes in patients with a poor diuretic response. Both diuretic dose and weight loss were higher in PROTECT.

In this subset of PROTECT, diuretic response was associated with both rehospitalization endpoints and mortality: 60-day HF rehospitalization: HR: 1.98 [95% CI 1.50-2.62], P<0.001; 60-day renal or cardiovascular rehospitalization: HR 1.67 [95% CI 1.34-2.08], P<0.001; 180-day mortality: 1.62 [95% CI 1.27-2.08], P<0.001. After adjustment for a well-calibrated prognostic model, diuretic response remained a predictor of rehospitalization endpoints (60-day HF rehospitalization: HR 1.61 [95% CI 1.16 – 2.23], p=0.004; 60-day renal or cardiovascular rehospitalization HR 1.42 (95% CI 1.11-1.81), p=0.005), but not mortality (HR 1.29 [95% CI 0.98-1.70], P=0.071). In contrast, hemoconcentration was predictive of 180-day mortality (HR 0.77 [95% CI 0.68 – 0.87], p<0.001), but did not contribute significantly to determining rehospitalization risk (60-day HF hospitalization: HR 0.92 [95% CI 0.79-1.07], P=0.285; 60-day renal or cardiovascular rehospitalization: HR 0.91 [95% CI 0.81-1.02], P=0.115). In EVEREST, after multivariable adjustment diuretic response was only predictive of 60-day heart failure hospitalization (HR 1.19 (95% CI 1.00-1.41), p=0.049). In EVEREST, hemoconcentration did not multivariably predict any of the outcomes (all p= n.s.). Study treatment did not show a significant effect on outcome or interactions with either diuretic response or hemoconcentration in any of the models.

Supplementary table S5 displays the gain in prediction (C-index) and improvement in reclassification in over the base clinical model in PROTECT and EVEREST. This shows a statistically significant, though very minor increase in C-statistic and improvement in reclassification for 60-day heart failure rehospitalization for PROTECT in particular; patterns are similar in both populations, although non-significant in EVEREST. In order to examine whether combining hemoconcentration and diuretic response could provide better risk stratification, we classified patients into groups, based on a diuretic response above (poor response) or below (good response) the median, and hemoconcentration above (good hemoconcentration) or below (poor hemoconcentration) the median. In both cohorts patients with a good diuretic response and poor hemoconcentration did not differ significantly in terms of clinical char-

Table 2a. Patient characteristics per tertile of diuretic response in PROTECT

Diuretic response (kg/40 mg Furosemide equivalent)	-1 [-1.4--0.8]	-0.4 [-0.5--0.3]	0 [-0.1-0]	P for trend
N =	**390**	**389**	**401**	
Demographics				
Sex (%(n) Male)	68.5 (267)	64.5 (251)	70.6 (283)	0.516
Age (years)	69.5±11.7	70.1±11	69.6±11.6	0.886
LVEF (%)	33.8 [25-41.8]	30 [20.2-40]	28 [20-38.2]	0.004
Systolic Blood Pressure (mmHg)	128.3±16.7	123.8±17.2	120.4±18.2	<0.001
Diastolic Blood Pressure (mmHg)	77.4±11.4	74.8±11.1	71.2±11.7	<0.001
Heart Rate (beats/min)	82.5±16.5	80.7±15.3	79.6±14.7	0.009
Rolofylline administration (%(n))	68.2 (266)	65.3 (254)	64.3 (258)	0.252
Clinical Profile				
Atrial fibrillation on presentation (%(n))	51.4 (76)	45 (68)	40.8 (71)	0.059
Orthopnea ≥ +2 (%(n))	96.4 (371)	96.6 (374)	95.2 (379)	0.409
Rales > 1/3 lung fields (%(n))	64.4 (251)	62.2 (242)	58.8 (235)	0.105
Edema ≥ +2 (%(n))	75.6 (295)	68.6 (267)	65.3 (262)	0.002
Jugular venous pressure ≥ 10 cm (%(n))	42.4 (142)	39.3 (138)	42.5 (159)	0.948
Medical History				
HF hospitalization (%(n))	94.9 (370)	95.9 (373)	95 (381)	0.93
Hypertension (%(n))	81 (316)	79.4 (309)	78.1 (313)	0.301
Diabetes Mellitus (%(n))	35.4 (138)	48.3 (188)	51.5 (206)	<0.001
Ischemic Heart Disease (%(n))	66.8 (260)	69.6 (270)	73.6 (295)	0.039
Myocardial Infarction (%(n))	46.5 (181)	46.5 (180)	54.6 (219)	0.022
CABG (%(n))	11.5 (44)	20.6 (79)	28.4 (114)	<0.001
Peripheral Vascular Disease (%(n))	10.3 (40)	9.8 (38)	12.7 (51)	0.27
Atrial Fibrillation (%(n))	60.1 (232)	51.4 (199)	54.5 (218)	0.119
ICD therapy (%(n))	7.2 (28)	14.1 (55)	22.2 (89)	<0.001
Stroke (%(n))	8.5 (33)	8 (31)	9.2 (37)	0.697
COPD (%(n))	17.7 (69)	18.5 (72)	20.9 (84)	0.243
Prior Medication Use				
ACE inhibitors or ARB (%(n))	76.7 (299)	76.6 (298)	73.1 (293)	0.238
Beta blockers (%(n))	67.7 (264)	78.7 (306)	82.8 (332)	<0.001
Mineralocorticoid Receptor Antagonists (%(n))	45.6 (178)	46.8 (182)	45.1 (181)	0.884
Laboratory Values				
Creatinine (mg/dL)	1.3 [1.1-1.6]	1.4 [1.1-1.8]	1.5 [1.2-1.9]	<0.001
eGFR (mL/min/1.73m2)	56±21.1	51.6±19.3	47.7±19.4	<0.001
Blood Urea Nitrogen (mg/dL)	26 [20-35.2]	29 [22-41]	35 [24-46.5]	<0.001
Sodium (mmol/L)	140.5 [138-143]	140 [137-143]	139 [136-141]	<0.001
Potassium (mmol/L)	4.4 [4-4.7]	4.3 [3.9-4.6]	4.1 [3.8-4.5]	<0.001
Hemoglobin (g/dL)	12.9 [11.5-14.3]	12.8 [11.4-14.1]	12.4 [11.2-13.9]	0.004

Table 2a. Patient characteristics per tertile of diuretic response in PROTECT (continued)

Diuretic response (kg/40 mg Furosemide equivalent)	-1 [-1.4--0.8]	-0.4 [-0.5--0.3]	0 [-0.1-0]	P for trend
BNP (mg/dL)	1234 [820-2423]	1300 [919.4-2393]	1335 [777.5-2366.3]	0.417
Outcomes				
Heart Failure Rehospitalization	7.4 (29)	12.3 (48)	20.2 (81)	<0.001
CV Rehospitalization	12.8 (50)	22.6 (88)	27.7 (111)	<0.001
Rehospitalization	15.6 (61)	27.2 (106)	32.4 (130)	<0.001
All-cause mortality	10.3 (40)	13.1 (51)	25.4 (102)	<0.001
Diuretic dose days 1-3	160 [120-220]	240 [179.7-400]	385 [234.9-720]	<0.001
Weight change days 1-4	-4.1 [-6--3]	-2.1 [-3.9--1.5]	-0.6 [-1.7-0.3]	<0.001
Diuretic response	-1 [-1.4--0.8]	-0.4 [-0.5--0.3]	0 [-0.1-0]	<0.001
Hemoconcentration (day 7)	0.4 [-0.3-1.1]	0.3 [-0.4-1]	0 [-0.7-0.7]	<0.001

Abbreviations: LVEF: left ventricular ejection fraction; HF: heart failure; CABG: coronary artery bypass graft; ICD: implantable cardiac defibrillator; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide.

Table 2b. Patient characteristics per tertile of diuretic response in EVEREST

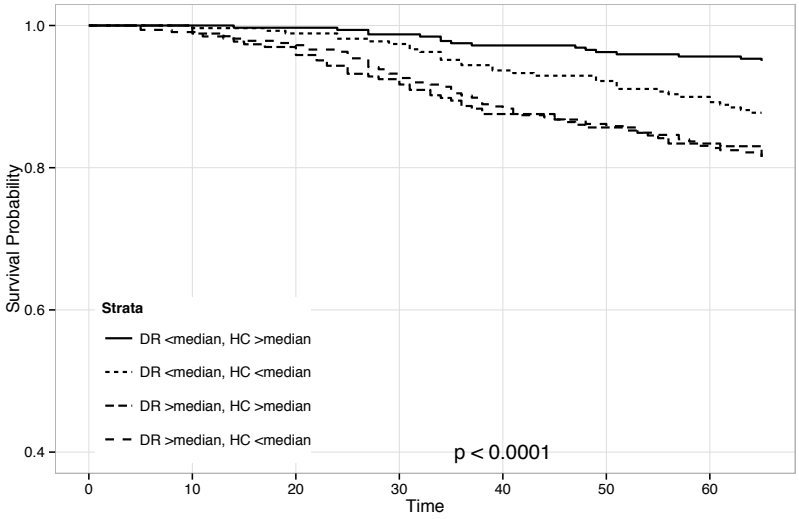
Diuretic response (kg/40 mg Furosemide equivalent)	-1.2 [-2--0.8]	-0.3 [-0.4--0.2]	0 [-0.1-0.2]	P for trend
N =	586	586	604	
Demographics				
Sex (%(n) Male)	76.3 (447)	75.6 (443)	71.4 (431)	0.051
Age (years)	64.8±11.3	65.4±11.4	65.1±11.4	0.605
LVEF (%)	30 [23.2-35]	30 [23-35]	28 [20-35]	<0.001
Systolic Blood Pressure (mmHg)	124.6±19.8	122.8±19.9	118.2±18.3	<0.001
Diastolic Blood Pressure (mmHg)	76.7±12.8	74.9±12.2	72.3±12.1	<0.001
Heart Rate (beats/min)	82.5±17.5	80.9±16	80.7±15.2	0.049
Tolvaptan administration (%(n))	49.1 (288)	46.4 (272)	48.2 (291)	0.744
Clinical Profile				
Atrial fibrillation on presentation	35.5 (208)	38.9 (228)	29.3 (177)	0.023
Orthopnea ≥ +2 (%(n))	51.1 (296)	57.4 (331)	55.8 (329)	0.113
Rales > 1/3 lung fields (%(n))	80.4 (467)	83.2 (480)	85 (503)	0.037
Edema ≥ +2 (%(n))	74.2 (435)	62.8 (368)	51.2 (309)	<0.001
Jugular venous pressure ≥ 10 cm (%(n))	28.9 (167)	30.5 (174)	28 (165)	0.723
Medical History				
HF hospitalization (%(n))	78.4 (458)	80.4 (469)	81.6 (491)	0.176
Hypertension (%(n))	72.4 (424)	69.6 (408)	70 (423)	0.382
Diabetes Mellitus (%(n))	32.9 (193)	38.6 (226)	36.4 (220)	0.215
Ischemic Heart Disease (%(n))	71.5 (414)	65.1 (372)	66.3 (398)	0.06
Myocardial Infarction (%(n))	51.9 (304)	49.1 (288)	50.8 (306)	0.723

Table 2b. Patient characteristics per tertile of diuretic response in EVEREST (continued)

Diuretic response (kg/40 mg Furosemide equivalent)	-1.2 [-2--0.8]	-0.3 [-0.4--0.2]	0 [-0.1-0.2]	P for trend
CABG (%(n))	11.4 (67)	15.5 (91)	19.7 (119)	<0.001
Peripheral Vascular Disease (%(n))	21.5 (126)	19.3 (113)	21.9 (132)	0.862
Atrial Fibrillation (%(n))	44 (258)	47.3 (277)	44.7 (270)	0.823
ICD therapy (%(n))	7.5 (44)	10.9 (64)	13.1 (79)	0.002
Stroke (%(n))	11.7 (67)	13.2 (76)	9.9 (59)	0.324
COPD (%(n))	7.5 (44)	6.7 (39)	10.9 (66)	0.032
Prior Medication Use				
ACE inhibitors or ARB (%(n))	85.3 (498)	87.7 (512)	84.4 (509)	0.66
Beta blockers (%(n))	69.5 (406)	67.6 (395)	68.8 (415)	0.8
Mineralocorticoid Receptor Antagonists (%(n))	63.7 (372)	61.8 (361)	59 (356)	0.099
Laboratory Values				
Creatinine (mg/dL)	1.2 [1-1.5]	1.2 [1-1.5]	1.3 [1-1.7]	<0.001
eGFR (mL/min/1.73m2)	59.5±20.1	56.4±20.6	54.3±21.1	<0.001
Blood Urea Nitrogen (mg/dL)	24 [18-32]	25 [19-34]	27 [20-36]	<0.001
Sodium (mmol/L)	140 [138-143]	140 [138-143]	140 [137-143]	0.01
Potassium (mmol/L)	4.4 [4-4.7]	4.3 [3.9-4.6]	4.2 [3.9-4.6]	<0.001
Hemoglobin (g/dL)	13.8 [12.5-14.9]	13.7 [12.3-15]	13.7 [12.1-14.9]	0.1
BNP (mg/dL)	711.5 [332.8-1528.6]	614 [259-1225]	684 [271.5-1345]	0.401
Outcomes				
Heart Failure Rehospitalization	6.1 (36)	7.5 (44)	12.3 (74)	<0.001
CV Rehospitalization	10.4 (61)	10.2 (60)	16.4 (99)	0.002
Rehospitalization	16.7 (98)	17.1 (100)	24.2 (146)	0.001
All-cause mortality	9.9 (58)	11.3 (66)	13.9 (84)	0.031
Diuretic dose days 1-3	70 [60-120]	180 [120-300]	180 [100-360]	<0.001
Weight change days 1-4	-2.8 [-4.6--1.6]	-1.5 [-2.5--0.9]	0 [-0.4-0.6]	<0.001
Diuretic response	-1.2 [-2--0.8]	-0.3 [-0.4--0.2]	0 [-0.1-0.2]	<0.001
Hemoconcentration (day 7)	0.4 [-0.3-1.2]	0.3 [-0.4-0.9]	0.1 [-0.6-0.7]	<0.001

Abbreviations: LVEF: left ventricular ejection fraction; HF: heart failure; CABG: coronary artery bypass graft; ICD: implantable cardiac defibrillator; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide.

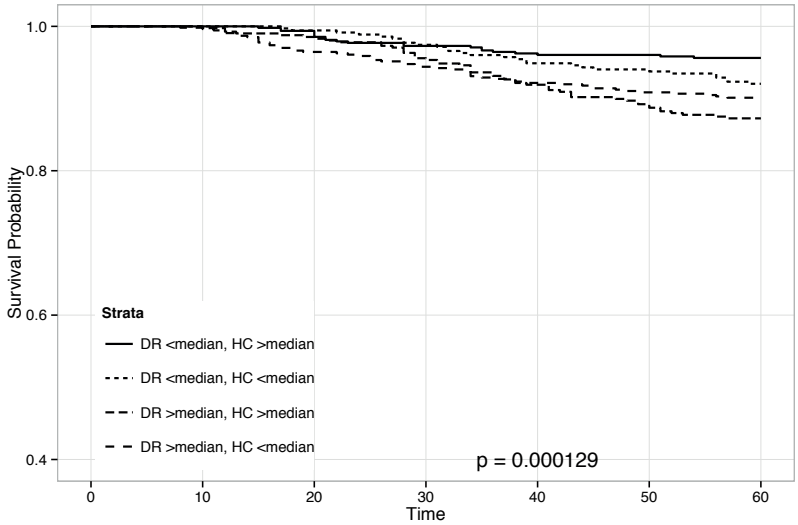
acteristics to patients with a good diuretic response and good hemoconcentration. Figures 1a (PROTECT) and 1b (EVEREST) display the Kaplan Meier curves for these groups, illustrating that patients who hemoconcentrate well in the presence of good diuretic response are at markedly lower risk of heart failure rehospitalization. Similarly, figure 2a (PROTECT) and 2b (EVEREST) illustrate the lower risk of renal and cardiovascular rehospitalization for patients with a good diuretic response and good hemoconcentration. Table 3 shows the significant additive value of hemoconcentration in the presence of good diuretic response to identify



DR <median, HC >median	321	321	320	317	312	309	307
DR <median, HC <median	269	269	266	262	252	248	242
DR >median, HC >median	265	265	257	245	232	227	221
DR >median, HC <median	325	322	317	303	288	280	270

Numbers at risk

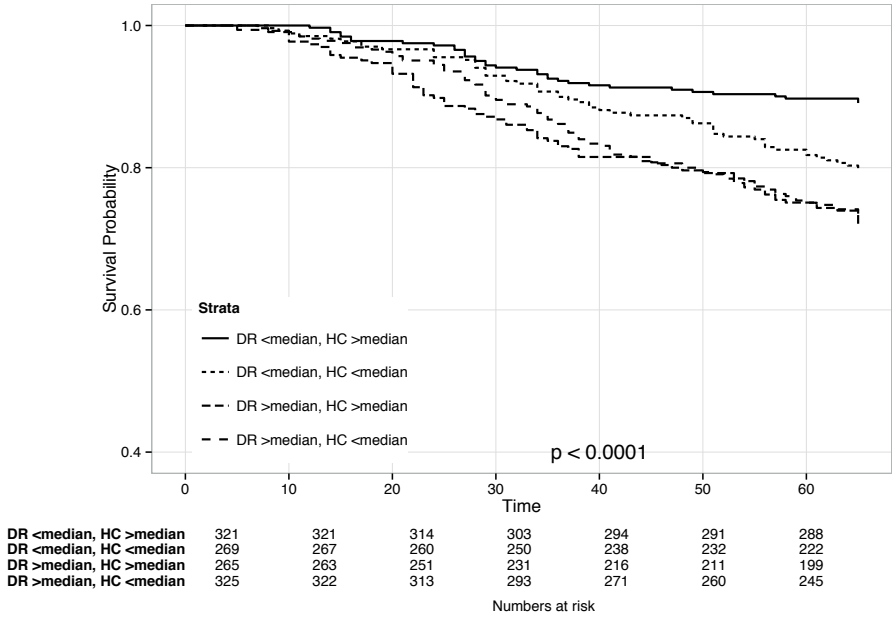
Figure 1a. Kaplan Meier survival curve for HF rehospitalization according to diuretic response and/or hemoconcentration above or below the median in PROTECT



DR <median, HC >median	480	480	477	467	462	461	459
DR <median, HC <median	352	352	350	343	334	331	324
DR >median, HC >median	408	408	402	390	375	364	356
DR >median, HC <median	536	535	517	506	494	487	483

Numbers at risk

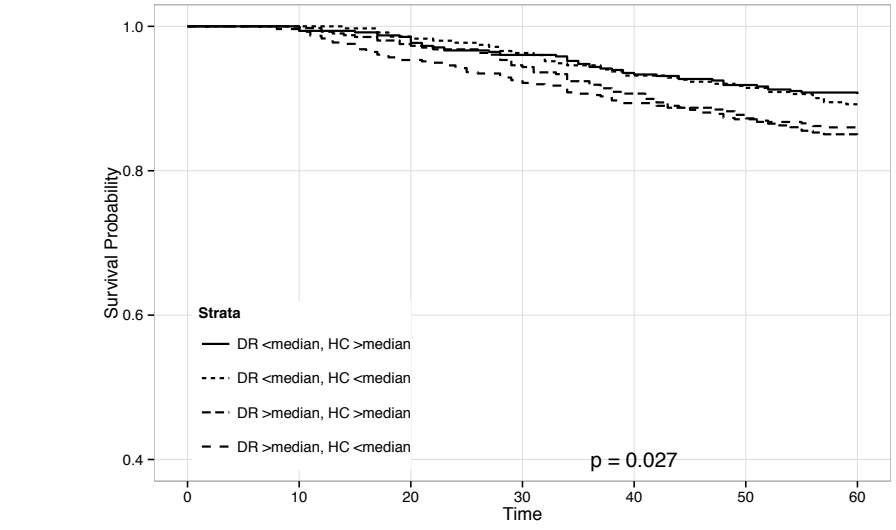
Figure 1b. Kaplan Meier survival curve for HF rehospitalization according to diuretic response and/or hemoconcentration above or below the median in EVEREST



DR <median, HC >median	321	321	314	303	294	291	288
DR <median, HC <median	269	267	260	250	238	232	222
DR >median, HC >median	265	263	251	231	216	211	199
DR >median, HC <median	325	322	313	293	271	260	245

Numbers at risk

Figure 2a. Kaplan Meier survival curve for renal or cardiovascular rehospitalization according to diuretic response and/or hemoconcentration above or below the median in PROTECT



DR <median, HC >median	480	480	473	461	449	441	436
DR <median, HC <median	352	352	347	339	328	323	314
DR >median, HC >median	408	408	398	386	370	358	347
DR >median, HC <median	536	534	511	496	479	467	461

Numbers at risk

Figure 2b. Kaplan Meier survival curve for cardiovascular rehospitalization according to diuretic response and/or hemoconcentration above or below the median in EVEREST

patients at low risk of heart failure hospitalization. This pattern remained after multivariable adjustment. There was no significant interaction between hemoconcentration en diuretic response. Patients with hemoconcentration and diuretic response above the median were about half as likely to be readmitted for HF compared with those without both of these responses to therapy (Table 4, p<0.05).

Table 3. Additive value of hemoconcentration in predicting 60-day HF rehospitalization in subgroups based on diuretic response

			Hemoconcentration per 1 unit increase		
	Subgroup		**Hazard ratio**	**95% CI**	**P-value**
PROTECT	Good diuretic response (<median)	Unadjusted	0.68	0.53-0.88	0.004
		Adjusted*	0.66	0.48-0.89	0.007
	Poor diuretic response (≥median)	Unadjusted	1.04	0.88-1.23	0.615
		Adjusted*	1.07	0.89-1.28	0.455
EVEREST	Good diuretic response (<median)	Unadjusted	0.79	0.63-1.01	0.060
		Adjusted*	0.79	0.61-1.01	0.061
	Poor diuretic response (≥median)	Unadjusted	1.10	0.93-1.31	0.276
		Adjusted*	1.03	0.85-1.25	0.782

**Adjusted for age, previous HF hospitalization, edema, systolic blood pressure, serum sodium, blood urea nitrogen (BUN), serum creatinine, albumin, hemoglobin, and study treatment*

Table 4. Risk of rehospitalization in patients with good diuretic response and good hemoconcentration versus all other patients

		Hazard Ratio*	**95% CI**	**P-value**
60-day HF rehospitalization	PROTECT	0.41	0.24-0.70	0.001
	EVEREST	0.53	0.34-0.84	0.007
60-day (renal or) cardiovascular rehospitalization	PROTECT	0.51	0.35-0.74	<0.001
	EVEREST	0.76	0.54-1.07	0.118

** adjusted for age, previous HF hospitalization, edema, Systolic blood pressure, serum sodium, Blood Urea Nitrogen (BUN), serum creatinine, albumin, hemoglobin, and study treatment*

DISCUSSION

The presence of hemoconcentration in addition to a good diuretic response allows for identification of patients at significantly lower risk of rehospitalization for acute heart failure. Thus, examining both decongestive markers may provide an easy accessible and relevant tool for clinicians to identify patients at particularly low risk of rehospitalization, with the potential for easing the burden on already overburdened health care systems.

Rehospitalization rates after an admission for acute heart failure are as high as 40% within 1 year, and 25% of patients are readmitted within 30 days.[14,15] This is a major problem and places an enormous strain on our health care system and costs. Identification of low risk patients is important, as early discharge and less frequent follow-up may be safe in this group of patients. Therefore, clinically applicable tools that can be used to identify low risk patients are sorely needed. Prediction of HF rehospitalization, however, even in the short term, remains a challenge. Using variables previously identified as strong outcome predictors in the PROTECT trial, reflecting a variety of important pathophysiological mechanisms (including renal dysfunction, low arterial blood pressure, serum albumin and sodium), only achieved modest accuracy, with C-indices around 0.70.[13] Diuretic response, a recently defined measure of decongestion, has been identified as a marker for prognosis, particularly short-term heart failure rehospitalization.[5,6] Diuretic response is a dynamic marker that encompasses complex mechanisms involved in response to diuretics, such as absorption, pharmacodynamics, and renin-angiotensin-system activation.[16] Hemoconcentration on the other hand is also a marker of decongestion, and may be seen as a correction of volume overload, in which diuretics restore euvolumia and hemoglobin levels rise as a result. Hemoconcentration has also been shown to be related to a lower risk of heart failure rehospitalization.[10]

As both diuretic response and hemoconcentration assess decongestion, we hypothesized that the combination of both provides additive value in predicting heart failure rehospitalization risk, which we initially analyzed in PROTECT and validated in EVEREST. In both populations, we found that patients who exhibited a good diuretic response and hemoconcentrated were at significantly lower risk of rehospitalization for HF. Even though the value of adding diuretic response and hemoconcentration to an established multivariable prediction model was limited, in patients with a good diuretic response, further assessment of hemoconcentration enables the clinician to identify a low risk patient. This combination suggests a profile of volume overload with an excellent response to therapy, thus achieving euvolemia. In contrast, poor hemoconcentration in patients with good diuretic response may reflect true volume overload with less efficient decongestion than suggested by weight loss. The patients with good diuretic response and hemoconcentration have a 50% lower risk of being rehospitalized after discharge, and therefore shorter hospital stay, and maybe even less frequent follow-up may be safe in this patient group. Both diuretic response and hemoconcentration are easily calculated using data collected during routine care, and are more accessible and applicable than elaborate risk models. For a clinician, evaluation of both diuretic response and hemoconcentration provides a simple assessment of risk of rehospitalization and may be used to tailor a patient's care. For instance, in the case of an acute heart failure patient with a favorable diuretic response, in which the clinician contemplates discharge, consequent assessment of hemoconcentration may help guide his decision. In the presence of hemoconcentration, this patient can be relatively safely discharged, with a low risk of heart failure rehospitalization. However, the absence of hemoconcentration may

trigger the clinician to re-evaluate his decision, and assess signs and symptoms again, and for instance prolong diuretic treatment for a while longer.

Overall, the associations were stronger in PROTECT than in EVEREST. There are a number of potential explanations. First, patients in PROTECT appear to have been sicker – older, more co-morbidities, more severe renal dysfunction, higher BNP levels and more signs of fluid overload. They also received more diuretics and lost more weight, lending support to this hypothesis. Finally, diuretic response was slightly better in PROTECT than in EVEREST.

Limitations

This study is a post-hoc analysis of two large randomized clinical trials, with all limitations as such. Additionally, the variables were only available in a subset of both trials, we therefore cannot rule out that the associations may be biased in this selected subgroup. Further validation of the combination of this metric in registries or beyond will have to show whether these results are translatable to 'real world' clinical care. However, we confirmed our findings in EVEREST, thus confirming the consistency of our results in another acute HF dataset. We did not have serial measurements of hemoglobin available, and therefore used discharge hemoglobin.

CONCLUSION

Both diuretic response and hemoconcentration are measures of decongestion and predict poor outcome in patients with acute HF. When good diuretic response co-exists with hemoconcentration the risk of short-term rehospitalization for HF was markedly lower, even following multivariable adjustment.

REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012; 33: 1787-1847.
2. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J, Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003; 24: 442-463.
3. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008; 29: 2388-2442.
4. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, Tang WH. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail. 2014; 7: 261-270.
5. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. Eur Heart J. 2014; 35: 1284-1293.
6. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G, Greenberg BH, Pang PS, Levin B, Hua TA, Severin T, Ponikowski P, Metra M, RELAX-AHF Investigators. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome-an analysis from RELAX-AHF. Eur J Heart Fail. 2014; 16: 1230-1240.
7. ter Maaten JM, Dunning AM, Valente MAE, Damman K, Ezekowitz JA, Califf RM, Starling RC, van der Meer P, O'Connor CM, Schulte PJ, Testani JM, Hernandez AF, Tang WHW, Voors AA. Diuretic response in acute heart failure - an analysis from ASCEND-HF. American Heart Journal. 2015; 170: 313-321.
8. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, Metra M, Davison BA, Givertz MM, Mansoor GA, Teerlink JR, Massie BM, Hillege HL, Voors AA. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. J Am Coll Cardiol. 2013; 61: 1973-1981.
9. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010; 122: 265-272.
10. Greene SJ, Gheorghiade M, Vaduganathan M, Ambrosy AP, Mentz RJ, Subacius H, Maggioni AP, Nodari S, Konstam MA, Butler J, Filippatos G, EVEREST Trial investigators. Haemoconcentration, renal function,

and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Eur J Heart Fail. 2013; 15: 1401-1411.

11. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JG, Givertz MM, Voors A, DeLucca P, Mansoor GA, Salerno CM, Bloomfield DM, Dittrich HC, PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med. 2010; 363: 1419-1428.
12. Konstam MA, Gheorghiade M, Burnett JC,Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007; 297: 1319-1331.
13. Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM, Davison BA, Mansoor GA, Ponikowski P, Voors AA, Cotter G, Metra M, Massie BM, O'Connor CM. Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: a report from the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) Study. Circ Heart Fail. 2014; 7: 76-87.
14. Krumholz HM, Lin Z, Keenan PS, Chen J, Ross JS, Drye EE, Bernheim SM, Wang Y, Bradley EH, Han LF, Normand SL. Relationship between hospital readmission and mortality rates for patients hospitalized with acute myocardial infarction, heart failure, or pneumonia. JAMA. 2013; 309: 587-593.
15. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, Barreto-Filho JA, Kim N, Bernheim SM, Suter LG, Drye EE, Krumholz HM. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA. 2013; 309: 355-363.
16. Ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol. 2015; 12: 184-192.

SUPPLEMENTARY MATERIAL

Supplementary table 1. In- and excluded patient population from PROTECT

Variable	Included patients	Excluded patients
N =	1180	853
Demographics		
Sex (% Male)	67.9 (801)	66 (563)
Age (years)	69.7±11.5	70.8±11.7
LVEF (%)	30 [22-40]	30 [20.5-40]
Systolic Blood Pressure (mmHg)	124.2±17.7	124.5±17.5
Diastolic Blood Pressure (mmHg)	74.4±11.7	72.7±12
Heart Rate (beats/min)	80.9±15.5	78.9±15.3
Rolofylline administration (%)	65.9 (778)	67.8 (578)
Clinical Profile		
Atrial fibrillation on presentation	45.5 (215)	35.6 (122)
Orthopnea (%)	96.1 (1124)	95.9 (796)
Rales (%)	61.7 (728)	59.8 (504)
Edema (%)	69.8 (824)	65.2 (551)
Jugular venous pressure (%)	41.4 (439)	39.5 (303)
Medical History		
HF hospitalisation (%)	95.3 (1124)	94.1 (803)
Hypertension (%)	79.5 (938)	79.4 (677)
Diabetes Mellitus (%)	45.1 (532)	45.7 (390)
Ischemic Heart Disease (%)	70 (825)	69.5 (592)
Myocardial Infarction (%)	49.3 (580)	49.5 (421)
CABG (%)	20.3 (237)	23.5 (199)
Peripheral Vascular Disease (%)	11 (129)	10.7 (91)
Atrial Fibrillation (%)	55.3 (649)	53.7 (454)
ICD therapy (%)	14.6 (172)	18 (153)
CRT (%)	9.2 (108)	11.7 (100)
Stroke (%)	8.6 (101)	9.6 (82)
COPD (%)	19.1 (225)	20.8 (177)
Prior Medication Use		
ACE inhibitors or ARB (%)	75.4 (890)	75.9 (644)
Beta blockers (%)	76.4 (902)	75.9 (644)
Mineralocorticoid Receptor Antagonists (%)	45.8 (541)	41 (347)
Laboratory Values		
Creatinine (mg/dL)	1.4 [1.1-1.8]	1.4 [1.1-1.8]
eGFR (mL/min/1.73m2)	51.7±20.2	51.4±19.9
Blood Urea Nitrogen (mg/dL)	29 [22-41]	30 [22-41.8]
Sodium (mmol/L)	140 [137-142]	140 [137-142]

Supplementary table 1. In- and excluded patient population from PROTECT (continued)

Variable	Included patients	Excluded patients
Potassium (mmol/L)	4.2 [3.9-4.6]	4.2 [3.8-4.6]
Hemoglobin (g/dL)	12.7 [11.3-14.1]	12.4 [11.1-13.8]
BNP (mg/dL)	1290.9 [835.1-2411.9]	1241.4 [818.5-1974]

Abbreviations: LVEF: left ventricular ejection fraction; HF: heart failure; CABG: coronary artery bypass graft; ICD: implantable cardiac defibrillator; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide.

Supplementary table 2. In- and excluded patient population from EVEREST

Variable	Included patients	Excluded patients
N =	1776	1809
Demographics		
Sex (% Male)	74.4 (1321)	74.7 (1352)
Age (years)	65.1±11.3	66.6±12.5
LVEF (%)	30 [22-35]	25 [20-32]
Systolic Blood Pressure (mmHg)	121.8±19.5	118.2±19.7
Diastolic Blood Pressure (mmHg)	74.6±12.5	70.1±12.6
Heart Rate (beats/min)	81.4±16.2	78.4±14.6
Tolvaptan administration (%)	47.9 (851)	51 (922)
Clinical Profile		
Atrial fibrillation on presentation	34.5 (613)	21.8 (392)
Orthopnea (%)	54.8 (956)	57.8 (1012)
Rales (%)	82.9 (1450)	81.8 (1441)
Edema (%)	62.6 (1112)	49 (885)
Jugular venous pressure (%)	29.1 (506)	26.7 (465)
Medical History		
HF hospitalisation (%)	80.2 (1418)	76.8 (1383)
Hypertension (%)	70.7 (1255)	71.8 (1298)
Diabetes Mellitus (%)	36 (639)	42.5 (769)
Ischemic Heart Disease (%)	67.7 (1184)	60.2 (1077)
Myocardial Infarction (%)	50.6 (898)	49.1 (887)
CABG (%)	15.6 (277)	27.8 (502)
Peripheral Vascular Disease (%)	20.9 (371)	21.5 (388)
Atrial Fibrillation (%)	45.3 (805)	40.7 (737)
ICD therapy (%)	10.5 (187)	20.5 (370)
Pacemaker therapy (%)	11.6 (206)	24.5 (444)
Stroke (%)	11.6 (202)	11.7 (211)
COPD (%)	8.4 (149)	12.4 (225)
Prior Medication Use		
ACE inhibitors or ARB (%)	85.8 (1519)	83 (1491)

Supplementary table 2. In- and excluded patient population from EVEREST (continued)

Variable	Included patients	Excluded patients
Beta blockers (%)	68.7 (1216)	73 (1311)
Mineralocorticoid Receptor Antagonists (%)	61.5 (1089)	48.1 (864)
Laboratory Values		
Creatinine (mg/dL)	1.2 [1-1.5]	1.3 [1.1-1.7]
eGFR (mL/min/1.73m2)	56.7±20.7	53.8±21.1
Blood Urea Nitrogen (mg/dL)	25 [19-34]	28 [20-38]
Sodium (mmol/L)	140 [137-143]	140 [137-142]
Potassium (mmol/L)	4.3 [4-4.7]	4.2 [3.8-4.5]
Hemoglobin (g/dL)	13.8 [12.3-15]	13.1 [11.7-14.5]
BNP (mg/dL)	667.2 [283-1396.8]	820 [333.4-1710.9]

Abbreviations: LVEF: left ventricular ejection fraction; HF: heart failure; CABG: coronary artery bypass graft; ICD: implantable cardiac defibrillator; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide.

Supplementary table 3. Trends in baseline characteristics across tertiles of hemoconcentration in PROTECT

Variable	-0.8 [-1.2--0.5]	0.2 [0-0.4]	1.3 [0.9-1.8]	P-trend
N =	393	388	399	
Demographics				
Sex (% Male)	65.4 (257)	67.5 (262)	70.7 (282)	0.111
Age (years)	69.5±12	69.8±11.3	69.8±11.1	0.74
LVEF (%)	30 [23-42]	30 [20-40]	30 [24-40]	0.948
Systolic Blood Pressure (mmHg)	124.4±17.3	124±18.4	124±17.4	0.745
Diastolic Blood Pressure (mmHg)	74.7±12	74.4±11.4	74.2±11.6	0.548
Heart Rate (beats/min)	82.1±16.4	79.8±14.4	80.8±15.6	0.22
Rolofylline administration (%)	63.9 (251)	67.3 (261)	66.7 (266)	0.408
Clinical Profile				
Atrial fibrillation on presentation	44.5 (65)	42 (63)	49.2 (87)	0.375
Orthopnea (%)	96.1 (374)	94.5 (364)	97.5 (386)	0.333
Rales (%)	62.1 (244)	59.5 (231)	63.6 (253)	0.665
Edema (%)	71.5 (281)	68 (264)	69.9 (279)	0.632
Jugular venous pressure (%)	42.3 (151)	38 (132)	43.8 (156)	0.681
Medical History				
HF hospitalisation (%)	95.2 (374)	95.4 (370)	95.2 (380)	0.962
Hypertension (%)	80.2 (315)	78.1 (303)	80.2 (320)	0.984
Diabetes Mellitus (%)	44.4 (174)	47.9 (186)	43.1 (172)	0.712
Ischemic Heart Disease (%)	69.2 (272)	71.8 (278)	69.1 (275)	0.969
Myocardial Infarction (%)	48.9 (192)	51.4 (199)	47.6 (189)	0.724
CABG (%)	20.1 (79)	20.3 (78)	20.4 (80)	0.915
Peripheral Vascular Disease (%)	11.3 (44)	10.8 (42)	10.8 (43)	0.84

Supplementary table 3. Trends in baseline characteristics across tertiles of hemoconcentration in PROTECT (continued)

Variable	-0.8 [-1.2--0.5]	0.2 [0-0.4]	1.3 [0.9-1.8]	P-trend
Atrial Fibrillation (%)	56.2 (219)	49.6 (192)	60.1 (238)	0.261
ICD therapy (%)	16.5 (65)	15.7 (61)	11.5 (46)	0.045
CRT (%)	7.9 (31)	9.5 (37)	10 (40)	0.303
Stroke (%)	7.9 (31)	9 (35)	8.8 (35)	0.658
COPD (%)	18.8 (74)	20.4 (79)	18 (72)	0.776
Prior Medication Use				
ACE inhibitors or ARB (%)	77.1 (303)	77.1 (299)	72.2 (288)	0.107
Beta blockers (%)	77.4 (304)	77.6 (301)	74.4 (297)	0.332
Mineralocorticoid Receptor Antagonists (%)	40.2 (158)	48.5 (188)	48.9 (195)	0.015
Laboratory Values				
Creatinine (mg/dL)	1.4 [1.1-1.8]	1.4 [1.1-1.8]	1.4 [1.1-1.7]	0.096
eGFR (mL/min/1.73m2)	50.4±19.4	51.7±21.6	53.1±19.6	0.062
Blood Urea Nitrogen (mg/dL)	32 [23-42]	30 [21-44]	27 [22-37]	<0.001
Sodium (mmol/L)	140 [137-142]	139 [136-142]	140 [138-143]	0.042
Potassium (mmol/L)	4.4 [4-4.8]	4.2 [3.8-4.6]	4.2 [3.9-4.6]	0.008
Hemoglobin (g/dL)	13 [11.6-14.6]	12.5 [11.3-13.9]	12.6 [11.3-13.9]	<0.001
BNP (mg/dL)	1300 [838.6-2303.3]	1346 [818-2405.7]	1220.5 [844.8-2423]	0.742

Abbreviations: LVEF: left ventricular ejection fraction; HF: heart failure; CABG: coronary artery bypass graft; ICD: implantable cardiac defibrillator; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide.

Supplementary table 4. Trends in baseline characteristics across tertiles of hemoconcentration in EVEREST

Variable	-0.7 [-1.2--0.4]	0.3 [0.1-0.5]	1.3 [1-1.9]	P-trend
N =	610	595	571	
Demographics				
Sex (% Male)	75.1 (458)	72.4 (431)	75.7 (432)	0.841
Age (years)	65.3±11.2	65.3±10.8	64.7±12.1	0.355
LVEF (%)	30 [23.2-35]	29 [22-35]	30 [22-35]	0.302
Systolic Blood Pressure (mmHg)	122.7±19.5	121.2±19.7	121.6±19.4	0.316
Diastolic Blood Pressure (mmHg)	74.6±12.8	74.1±12.2	75.1±12.5	0.448
Heart Rate (beats/min)	80.4±15.4	81.2±16.9	82.6±16.4	0.017
Tolvaptan administration (%)	49.7 (303)	47.4 (282)	46.6 (266)	0.286
Clinical Profile				
Atrial fibrillation on presentation	33.4 (204)	33.9 (202)	36.3 (207)	0.314
Orthopnea (%)	53.3 (319)	53.5 (313)	57.7 (324)	0.136
Rales (%)	82.3 (494)	82.5 (485)	83.8 (471)	0.509
Edema (%)	62.2 (379)	62.2 (370)	63.6 (363)	0.638
Jugular venous pressure (%)	28.5 (170)	29.7 (173)	29.2 (163)	0.778

Supplementary table 4. Trends in baseline characteristics across tertiles of hemoconcentration in EVEREST (continued)

Variable	-0.7 [-1.2--0.4]	0.3 [0.1-0.5]	1.3 [1-1.9]	P-trend
Medical History				
HF hospitalisation (%)	79.6 (483)	81.3 (482)	79.6 (453)	0.973
Hypertension (%)	73.3 (447)	70.1 (417)	68.5 (391)	0.069
Diabetes Mellitus (%)	36.4 (222)	37.1 (221)	34.3 (196)	0.468
Ischemic Heart Disease (%)	69.7 (421)	67.7 (397)	65.4 (366)	0.114
Myocardial Infarction (%)	51.3 (313)	51.6 (307)	48.9 (278)	0.406
CABG (%)	16.6 (101)	16.1 (96)	14 (80)	0.231
Peripheral Vascular Disease (%)	20.2 (123)	21.2 (126)	21.4 (122)	0.608
Atrial Fibrillation (%)	44.3 (270)	45.4 (270)	46.4 (265)	0.459
ICD therapy (%)	10.7 (65)	10.9 (65)	10 (57)	0.712
Pacemaker therapy (%)	12 (73)	11.6 (69)	11.2 (64)	0.684
Stroke (%)	12 (71)	11.7 (69)	11.1 (62)	0.634
COPD (%)	9.7 (59)	7.7 (46)	7.7 (44)	0.218
Prior Medication Use				
ACE inhibitors or ARB (%)	84.9 (517)	87.6 (521)	84.8 (481)	0.998
Beta blockers (%)	68.3 (416)	68.6 (408)	69.1 (392)	0.761
Mineralocorticoid Receptor Antagonists (%)	59.4 (362)	62.2 (370)	63 (357)	0.212
Laboratory Values				
Creatinine (mg/dL)	1.2 [1-1.5]	1.2 [1-1.6]	1.2 [1-1.5]	0.075
eGFR (mL/min/1.73m2)	55.8±20.6	56.2±20.9	58.3±20.6	0.037
Blood Urea Nitrogen (mg/dL)	26 [20-36]	25 [19-33.5]	24 [19-32]	<0.001
Sodium (mmol/L)	140 [137-142]	140 [137-143]	140 [138-143]	0.078
Potassium (mmol/L)	4.3 [4-4.7]	4.3 [4-4.7]	4.2 [3.9-4.6]	0.108
Hemoglobin (g/dL)	14 [12.6-15.2]	13.6 [12.1-14.8]	13.6 [12.2-14.8]	<0.001
BNP (mg/dL)	531.5 [231.2-1302.9]	601 [260.9-1348.5]	827 [414.5-1550.9]	0.795

Abbreviations: LVEF: left ventricular ejection fraction; HF: heart failure; CABG: coronary artery bypass graft; ICD: implantable cardiac defibrillator; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide.

Supplementary table 5. Prognostic performance of diuretic response and hemoconcentration in PROTECT and EVEREST

	C-index	Gain in C-index	P-value	NRI	P-value
PROTECT					
60-day HF rehospitalization					
Base model*	0.71				
Add diuretic response	0.72	1.4%	0.003	0.25	0.03
Add hemoconcentration	0.72	0.7%	0.284	0.03	0.58
Add diuretic response & Hemoconcentration	0.73	1.6%	0.009	0.27	0.01

Supplementary table 5. Prognostic performance of diuretic response and hemoconcentration in PROTECT and EVEREST (continued)

	C-index	Gain in C-index	P-value	NRI	P-value
60-day renal or cardiovascular					
Base model*	0.66				
Add diuretic response	0.67	1.2%	0.005	0.22	0.02
Add hemoconcentration	0.66	0.7%	0.302	0.00	0.79
Add diuretic response & Hemoconcentration	0.67	1.5%	0.015	0.30	0.01
180-day mortality					
Base model*	0.73				
Add diuretic response	0.73	0.5%	0.058	0.27	0.15
Add hemoconcentration	0.74	0.9%	<0.001	0.18	0.09
Add diuretic response & Hemoconcentration	0.74	1.2%	<0.001	0.28	0.01
EVEREST					
60-day HF rehospitalization					
Base model*	0.71				
Add diuretic response	0.72	1.0%	0.028	0.14	0.18
Add hemoconcentration	0.7q	0.3%	0.246	-0.05	0.97
Add diuretic response & Hemoconcentration	0.71	1.1%	0.056	0.09	0.26
60 day CV rehospitalization					
Base model*	0.66				
Add diuretic response	0.66	0.2%	0.175	0.03	0.45
Add hemoconcentration	0.66	0.0%	0.289	0.12	0.19
Add diuretic response & Hemoconcentration	0.66	0.3%	0.293	0.12	0.08
180-day mortality					
Base model*	0.70				
Add diuretic response	0.70	0.2%	0.302	0.10	0.26
Add hemoconcentration	0.70	-0.1%	0.583	0.03	0.46
Add diuretic response & Hemoconcentration	0.70	0.2%	0.524	0.11	0.18

*Base model includes age, previous HF hospitalization, edema, systolic blood pressure, serum sodium, blood urea nitrogen (BUN), serum creatinine, albumin, hemoglobin, and study treatment